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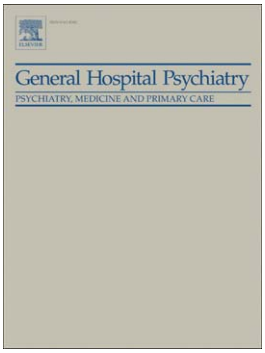

Chronic Obstructive Pulmonary Disease and anxiety disorders: A nationwide population-based study in Taiwan

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1)Title page

Title

Chronic Obstructive Pulmonary Disease and anxiety disorders: A nationwide population-based study in Taiwan.

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Running title

Chronic Obstructive Pulmonary Disease and anxiety disorders in Taiwan

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2)Abstract

Objective: Few studies have investigated the relationship between Chronic Obstructive Pulmonary Disease (COPD) and anxiety disorder outcomes. We sought to investigate the association in a large national sample.

Methods: Cases were identified from Taiwan's National Health Insurance Research Database who were aged 15 years and above, with a new primary diagnosis of COPD (ICD-9:491, 492, 494 and 496) between 2000 and 2007. The 29,951 cases identified were compared to 29,951 controls matched on sex, age, urban/rural residence and socioeconomic status based on insurance premium. Both groups were followed until the end of 2008 for instances of anxiety disorders. Competing risk adjusted Cox regression analyses were applied, adjusting for matching variables, Charlson comorbidity index, hospital admission days and daily dose of prednisone.

Results: Of the 59,902 subjects, 3951 were found to have anxiety disorders during a mean (SD) follow-up period of 5.5 (2.5) years. COPD, female, urban residence, lower dose of prednisone use, depressive disorders and higher outpatient visits were independent predictors of incident anxiety disorder.

Conclusions: COPD was associated with increased risk of an anxiety disorder diagnosis, independent of a number of potential confounding factors.

Key words

Chronic Obstructive Pulmonary Disease, Anxiety, Prednisone, Charlson comorbidity index, Nationwide, Cohort

3)Text

Introduction

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by airflow limitation with a progressive and not fully reversible course [1]. COPD affects 329 million people or nearly 5% of the population worldwide. In 2011, it ranked as the fourth leading cause of death, killing over 3 million people[2]. COPD also impairs daily activities, social functioning, and quality of life, and is associated with increased healthcare costs due to its complex psychological comorbidities, and lengthy disease course[3, 4]. Among psychological comorbidities, depression and anxiety [5-7] are frequent, and more common in patients with COPD than the general population[8]. Although the relationships between COPD and anxiety have been considered, most research has been limited to cross-sectional studies of relatively small samples and use of screening questionnaires rather than physician diagnoses. A recent systematic review cited ten studies that had diagnosed anxiety disorders from a clinical interview using DSM-IV or previous versions of DSM, or ICD-10 [9]. This article concluded that the prevalence of clinical anxiety in patients with COPD ranged from 10~55% among in-patients, and 13~46% among out-patients. However, among these studies, only four used comparison groups, suggesting raised prevalence in COPD [10-13]. In Asia , a recent case-control study [14] found a 3-fold higher risk of anxiety disorder in COPD than controls (18.3% vs 5.3%) in China, but no population-based cohort study has yet been reported in Asia. In addition, the association of prednisone with anxiety remains controversial with inconsistent results[15-18] with previous studies limited by cross-sectional design and small sample sizes. We describe what we believe to be

the first Asian population-based cohort study to investigate the role of COPD in the subsequent development of anxiety disorder, as well as the first population-based cohort study to investigate the association between prednisone and anxiety.

Material and methods

Sample

A retrospective cohort study was assembled using data from the Taiwan National Health Insurance Research Database (NHIRD) provided by that country's National Health Research Institute (NHRI) which included outpatient, ambulatory, hospital inpatient care, as well as dental services. The National Health Insurance (NHI) program provides compulsory universal health insurance, implemented from March 1995, covering all delivery of health care in 98% of the national population. In cooperation with the Bureau of NHI, the NHRI extracted a randomly sampled representative database of 1,000,000 people from the year 2005 registry of all NHI enrollees using a systematic sampling method for research purposes, forming the Longitudinal Health Insurance Database (LHID). There are no statistically significant differences in age, sex, or health care costs between this sample and all enrollees [19].

COPD cases were identified based on recorded International Classification of Disease, Ninth revision (ICD-9) codes of 491, 492, 494 and 496. All medical claims made under this diagnostic code during 1997 to 2008 were collected from NHIRD for further analysis. The definition of COPD for this analysis required an inpatient diagnosis and/or at least one year's duration of diagnosed COPD from outpatient services, a definition consistent with other research using this database [20]. To define new cases, people who had received any COPD diagnosis in the medical claim data from 1997 to 1999 were excluded from the analysis. In this way, 29,951 new COPD cases aged more than 15 years were identified. For assessing the association between COPD and anxiety disorder risk, one control per case was randomly sampled from the remaining sample, matching for sex, age within 1 year, urban/rural residence and insurance premium (a marker of socioeconomic status; see below). Both cases and controls were followed for diagnosed anxiety disorder as an outcome. Anxiety disorders were defined in this study on the basis of ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23 and 300.3. All study patients without anxiety disorder diagnosis before the index date. The index date was the first COPD diagnosis date, and this was also assigned to the respective matched controls, who were NHI enrollees without an anxiety disorder diagnosis before the index date.

Covariates considered in this analysis included age, sex, area of residence (urban/rural), insurance premium, prednisone use, Charlson comorbidity index and hospital admission days. The insurance premium served as an indicator of economic status and was classified into one of three categories: fixed premium and dependent, monthly income less than 20,000 New Taiwan Dollars (NTD), and NTD 20,000 or more (1US $ = 32.1 NTD in 2008). The fixed premium group comprised those requiring social welfare support, which included low-income citizens and veterans. The 'dependent' insurance group referred to family members who did not have a fixed salary income. Only prednisone use for at least one year was classified as use. The annual average cumulative defined daily dose (DDD) of prednisone was calculated and divided into 3 groups (0, 1-29, 30+). The defined daily dose recommended by the WHO is a unit for assessing the standard dose of drug. Cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDDs of a drug within a time period. The annual average cumulative DDD was used to assess the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index which comprises a summation of diseases weighted on the basis of their association with mortality [21] as of the index date. "Hospital admission days"

for any disorder during any period was also included as an indicator of general health. The Charlson comorbidity index and hospital admission days were measured prior to the outcome since 1997.

Statistical analysis

Death prior to anxiety disorder was considered as a competing risk event. The death date was retrieved from the national mortality database. The death-adjusted cumulative incidences of anxiety disorder were calculated using the Fine and Gray method [22]. Each person's first presentation within the study period was used in the calculation of outcome risk over given time intervals. The risk of anxiety disorder during the follow-up period was calculated using survival analysis, with the time function represented by the number of years from the index date of COPD diagnosis to December 31, 2008 (end of follow-up) or until the date of death or migration if earlier. Competing risk adjusted Cox regression models [22] were fitted to estimate associations between COPD and anxiety disorder, adjusting for covariates. All data management was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package "cmprsk" [23].

Time-dependent Cox regression model was used for multivariate assessment of prednisone use on anxiety disorder by controlling the potential confounding covariates. Instead of modeling prednisone as a cumulative effect by calculating the cumulative annual average DDD during the follow-up period, time-dependent model can take dynamic changing of prednisone use into account by assessing the yearly DDD of prednisone use effect during the following period in this study. Hazard ratios (HRs) and 95% confidence interval (CI) for bipolar were reported and comparing to the main analysis.

We classified anxiety diagnosis as two categories: (1) 300.0 (anxiety state) (2) 'specified anxiety', including 300.01(panic disorder), 300.02(generalized anxiety disorder), 300.2(phobic disorders), 300.21(agorophobia), 300.23(social anxiety disorder) and 300.3(obsessive-compulsive disorder). Besides, we also classified anxiety diagnosis as 'diagnosed by psychiatrist' and 'diagnosed by other physician'. The frequency of these two kinds of classification was reported. In order to reveal these diagnosis effects on our results, we performed sensitivity analysis which only focused on 'specified anxiety' and 'diagnosed by psychiatrist', respectively. The anxiety state and 'diagnosed by other physician' type of anxiety were considered as competing event and adjusted by competing Cox regression model.

Results

The two cohorts consisted of 29,951 people with newly-diagnosis COPD and 29,951 matched controls ascertained from the database covering 2000-2007. Cohort characteristics are described and compared in Table 1. Of the COPD cases, 60% were male and highest numbers were in the 65+ year range. More

than 70% were urban residents and one-third were receiving social welfare support or were dependent on their family. The COPD cohort used steroid during follow-up more frequently than the control cohort. The mean Charlson comorbidity index, hospital admission days and outpatient visits were higher in the COPD cohort than in the control cohort (T-test $p<0.001$).

Insert Table 1 here

Of the total 59,902 subjects, 3951 received a diagnosis of an anxiety disorder during the surveillance period: 2735 (9.13%) in the COPD cohort and 1216 (4.06%) in the control cohort. The mean (SD) follow-up interval for all subjects was 5.5 (2.5) years (Table 1). The anxiety disorder incidence for the COPD cohort was 1674.3 per 10^5 person-years (95% CI: 1612.1-1738.3) and that for the control cohort was 744.4 per 10^5 person-years (95% CI: 703.2-787.5). Kaplan-Meier analysis of cumulative incidence showed that patients with COPD had a significantly higher rate of incident anxiety disorders than the non-COPD group ($p < 0.001$; modified log-rank test) (Figure 1).

Insert Figure 1 here

Analyses of associations of interest are summarized in Table 2. In the fully

adjusted Cox regression model from the competing risk analysis, COPD was positively associated with anxiety disorder (HR 2.50, 95% CI 2.33-2.69, p<0.001). Additional factors associated with anxiety disorder incidence were female, urban residence, lower dose of prednisone use, depressive disorders and higher outpatient visits.

Insert Table 2 here

Factors associated with anxiety disorder incidence among the COPD cohort were similar with the main finding of all study patients' analysis (Table 3). In the stratified analyses, associations of interest were significant on the basis of sex and age in the fully adjusted Cox regression models (Table 4). The interaction were significant of COPD by gender and COPD by age group (both P<0.001).The negative association results between prednisone use and anxiety disorder were similar both in cumulative effect analysis (Table 3) and yearly dynamic effect time-dependent analysis (Table 5).

Of 3951 anxiety events in our main analysis, 3527 (89.27%) for anxiety state diagnosis and 424 (10.73%) for specified anxiety; 3360 (85.04) diagnosed by other physician and 591 (14.96%) diagnosed by psychiatrist. When we focused on specified anxiety diagnosis as interest event and considered anxiety

state as competing event to perform competing Cox regression analysis, the COPD was also positive associated with anxiety, adjusted hazard ratio=2.51, 95% CI:2.01-3.14. Besides, the sensitivity analysis which focused on anxiety diagnosed by psychiatrist was also similar to the main analysis, adjusted hazard ratio=2.32, 95% CI:1.92-2.80.

Insert Table 3 here

Insert Table 4 here

Insert Table 5 here

Discussion

To our knowledge, our study is the first nationwide population-based cohort study to investigate specifically the association between COPD and the risk of subsequent anxiety disorders in an Asian population. The cumulative incidence of anxiety disorder in a cohort of newly diagnosed COPD remained higher than in a non-COPD matched comparison group over a mean follow-up period of 5.5 years (Table 1) with an unadjusted hazard ratio of 2.21. After further adjusting for a number of potential confounding factors, the hazard ratio remained little changed at 2.22 (HR 2.22; 95% CI 2.07 to 2.38). The finding is similar to that of

cross-sectional studies, showing that anxiety disorders are highly prevalent among COPD-participants with a prevalence two to three times higher than among non-COPD participants [10, 13, 14, 24, 25]. Compared to the finding of Wagena's Maastricht Study [26], a prospective population-based cohort study set up among Dutch employees to investigate the association of COPD and subsequent anxiety, our association was not as strong as their odds ratio of 5.09 (95% CI 2.91 to 8.89) for COPD and risk of anxiety (after controlling for sex, age, educational level and smoking status). Asian patients have been found to be more unwilling than Western patients to reveal or admit feelings of anxiety due to perceived stigma of mental illness, which may have given rise to a relative lower risk [27].

We also found that that female COPD patients are more likely than men to have anxiety, which is consistent with reports from previous studies [14, 28, 29]. In addition, an overlap between anxiety and depressive symptoms in patients with COPD is common and may increase the prevalence of patients with anxiety disorder [30, 31], although in our study COPD remained associated with an increased risk of anxiety disorder even after adjusting for depression.

Our study is also the first study to evaluate the association between prednisone use and anxiety in a national sample, finding negative association between the

dose of prednisone and the development of anxiety disorders in COPD. Previous study showed COPD patients receiving prednisone treatment had significant improvements in dyspnea [32] and this might be linked to lower anxiety. Although an animal study reported that prednisone causes anxiety-like behaviors, suggesting that altered gene expressions related to hippocampal remodeling or damage are involved in such behavioral changes [33], previous human studies have given rise to inconsistent results over the relationship of prednisone use and anxiety in asthma. Three studies have reported that anxiety was associated with increased use of prednisone[15-17] while other two studies found no significant relationship[18, 34]. However, most were limited by cross-sectional designs and/or small sample sizes.

It remains unclear why there is a high prevalence of anxiety in patients with COPD. The causal pathway between COPD and anxiety is complex, overlapping and maybe bidirectional[35] . Several theories have been proposed to explain the association. In Pumar's review article, shortness of breath (hyperventilation), the main symptom of COPD, can lower pCO_2 and cause respiratory alkalosis. This pattern of breathing (dyspnea) is usually a source of anxiety and consequently evokes panic attacks. In turn, it is possible to evoke symptoms of dyspnea in panic disorder patients when infusing lactate or inhaling excessive CO_2 [36]. In

addition, cerebral hypoxia is probably involved in the causation of symptoms of anxiety in sufferers of COPD[37]. Brain image studies also suggest a shared etiology between anxiety and dyspnea, and dyspnea is processed in the same brain areas (amygdala and wider limbic system) that process fear and anxiety [38, 39]. Cognitive behavior models offer another important theory. Clark's model proposes that normal bodily sensations are catastrophically misinterpreted as dyspnea by patients with panic disorder, causing a consequent panic attack [40]. Furthermore, patients with COPD often have comorbid depression and an overlap between depressive and anxiety symptoms is common. Thus, depression itself may play a significant role to increase the prevalence of anxiety disorder in patients with COPD.

This study had several strengths. Most previous studies addressing comorbid anxiety in patients with COPD have been cross-sectional which does not allow conclusions to be drawn about the temporal relationship between COPD and anxiety disorders. In addition, research to date has been predominantly confined to Western populations, as well as having small sample sizes and lacking control groups, thus limiting wider generalizability. Our study addressed these limitations. Nonetheless, there are also important limitations, particularly arising from the use of routine data, such as lack of information on

other important potential confounders, including stressful life events, family history, and especially smoking history. The diagnosis for COPD and anxiety disorders was based on the physicians' diagnosis and measurement bias cannot be excluded. In addition, we were not able to assess the relationships between the severity of COPD and the level of anxiety disorder, due to lack of data. In regard to the association of prednisone and anxiety disorders, the level of prednisone use were defined by Defined Daily Dose which does not allow medication patterns to be examined such as whether prednisone was received long-term or short-term, on a daily basis or in intermittent. In addition, more than 90% of the sample falls into the lowest prednisone dose category. This leaves considerable potential for residual confounding when used as a covariate.

Conclusion

Our findings from a national health insurance dataset found a link between COPD and anxiety disorders. Given the high and rising prevalence of COPD, clinicians need to be particularly aware of the occurrence of anxiety disorder and psychological or pharmacological interventions should be initiated. Further research is needed to explore underlying mechanisms linking these two adverse health outcomes.

4) Acknowledgments

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5) Disclosures

Conflicting interests

None.

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Table 1 Characteristics of COPD cases and their matched [a] controls in Taiwan, 2000-2007.

Characteristic		COPD		Non-COPD[a]		Chi-square test p value
		N	%	N	%	
Sex						
	Female	11945	39.88	11945	39.88	>0.99
	Male	18006	60.12	18006	60.12	
Age group , year						
	15-24	1022	3.41	1022	3.41	>0.99
	25-44	5371	17.93	5371	17.93	
	45-64	10873	36.3	10873	36.3	
	65+	12685	42.35	12685	42.35	
Age, year (mean±SD)		59.05±16.69		59.02±16.65		0.789
Residence						
	Rural	8845	29.53	8845	29.53	>0.99
	Urban	21106	70.47	21106	70.47	
Insurance premium						
	Fixed premium and dependent	9364	31.26	9364	31.26	>0.99
	Less than NTD [b] 20,000	7782	25.98	7782	25.98	
	NTD 20,000 or more	12805	42.75	12805	42.75	
Prednisone, Define Daily Dose (DDD)						
	0	9963	33.26	17493	58.41	<0.001
	1-29	11171	37.30	9598	32.05	
	30+	8817	29.44	2860	9.55	
Anxiety disorder [c]						
	No	27216	90.87	28735	95.94	<0.001
	Yes	2735	9.13	1216	4.06	
Depression disorder [d]						
	No	28903	96.5	29411	98.2	<0.001
	Yes	1048	3.5	540	1.8	
Charlson index (mean±SD)		1.98±2.13		1.17±1.81		<0.001
Hospital admission days (days, mean±SD)		14.61±90.55		6.66±56.79		<0.001
Outpatient (visits, mean±SD)		26.01±20.49		15.64±16.05		<0.001

[a]Matched by sex and age (±1 years old).

[b] 1 USD = 32.1 NTD in 2008

[c]ICD-9:300.0,300.01,300.02,300.2,300.21,300.23,300.3.

[d]ICD-9: 296.20~296.36, 296.82, 300.4, 311

Table 2 Competing risk adjusted Cox regression analysis on anxiety disorder in Taiwan, 2000-2007

Variable		Unadjusted hazard ratio		Adjusted hazard ratio	
		Estimate (95% CI [a])	P value	Estimate (95% CI [a])	P value
COPD					
	No	1.00		1.00	
	Yes	2.21 (2.06-2.36)	<0.001	2.50 (2.33-2.69)	<0.001
Sex					
	Female	1.00		1.00	
	Male	0.59 (0.55-0.62)	<0.001	0.65 (0.61-0.69)	<0.001
Age (10 years)		1.03 (1.01-1.04)	0.002	1.02 (1.00-1.03)	0.129
Residence					
	Rural	1.00		1.00	
	Urban	1.08 (1.01-1.15)	0.031	1.15 (1.07-1.24)	<0.001
Insurance premium					
	Fixed premium and dependent	1.00		1.00	
	Less than NTD [b] 20,000	0.93 (0.87-1.00)	0.057	0.93 (0.86-1.02)	0.113
	NTD 20,000 or more	0.97 (0.91-1.03)	0.347	0.99 (0.91-1.07)	0.749
Prednisone, DDD [c]					
	0	1.00		1.00	
	1-29	0.58 (0.54-0.62)	<0.001	0.43 (0.40-0.47)	<0.001
	30+	0.38 (0.34-0.42)	<0.001	0.21 (0.19-0.23)	<0.001
Depression disorder [d], yes		2.70 (2.37-3.08)	<0.001	2.43 (2.18-2.72)	<0.001
Charlson comorbidity index		1.04 (1.03-1.05)	<0.001	0.93 (0.80-1.08)	0.179
Hospital admission days (100 days)		0.94 (0.83-1.06)	0.291	0.94 (0.79-1.10)	0.191
Outpatient (10 visits)		1.19 (1.17-1.20)	<0.001	1.21 (1.19-1.23)	<0.001

[a]CI: Confidence interval.

[b] 1USD = 32.1 NTD in 2008

[c] DDD: Define daily dose

[d]ICD-9: 296.20~296.36, 296.82, 300.4, 311

Table 3 Competing risk adjusted Cox regression analysis on anxiety disorder among COPD patients in Taiwan, 2000-2007

Variable	Unadjusted hazard ratio		Adjusted hazard ratio	
	Estimate (95% CI [a])	P value	Estimate (95% CI [a])	P value
Sex				
Female	1.00		1.00	
Male	0.61 (0.57-0.66)	<0.001	0.69 (0.64-0.75)	<0.001
Age (10 years)	1.00 (0.98-1.02)	0.967	1.01 (0.98-1.03)	0.669
Residence				
Rural	1.00		1.00	
Urban	1.08 (0.99-1.17)	0.074	1.18 (1.08-1.29)	<0.001
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD [b] 20,000	0.93 (0.85-1.01)	0.101	0.92 (0.83-1.02)	0.130
NTD 20,000 or more	1.02 (0.94-1.10)	0.675	0.99 (0.90-1.09)	0.807
Prednisone, DDD [c]				
0	1.00		1.00	
1-29	0.43 (0.39-0.46)	<0.001	0.39 (0.36-0.43)	<0.001
30 +	0.24 (0.21-0.26)	<0.001	0.20 (0.17-0.22)	<0.001
Depression disorder [d]	2.23 (1.92-2.59)	<0.001	2.31 (2.04-2.61)	<0.001
Charlson comorbidity index	0.99 (0.97-1.00)	0.142	0.93 (0.78-1.09)	0.251
Hospital admission days (100 days)	0.80 (0.61-1.04)	0.092	0.98 (0.83-1.14)	0.212
Outpatient (10 visits)	1.14 (1.12-1.15)	<0.001	1.19 (1.17-1.21)	<0.001

[a]CI: Confidence interval.

[b] 1USD = 32.1 NTD in 2008

[c] DDD: Define daily dose

[d]ICD-9: 296.20~296.36, 296.82, 300.4, 311

Table 4 Association between COPD and anxiety disorder by gender and age group, 2000-2007

Subgroup	Adjusted hazard ratio on anxiety disorder	
	Estimate (95% CI[b])	P value
Total	2.50 (2.33-2.69)	<0.001
Sex		
Male	2.81 (2.52-3.13)	<0.001
Female	2.25 (2.04-2.49)	<0.001
Age group		
15-24	3.68 (1.88-7.24)	<0.001
25-44	2.81 (2.30-3.44)	<0.001
45-64	2.33 (2.09-2.61)	<0.001
65+	2.51 (2.24-2.81)	<0.001

[a]Competing risk adjusted Cox regression analysis controlling by gender, age, residence, insurance premium, prednisone, depression disorder (ICD-9: 296.20~296.36, 296.82, 300.4, 311), Charlson comorbidity index, hospital admission days, outpatient visits and mortality.

[b]CI: Confidence interval.

Table 5 Time dependent Cox regression analysis on anxiety disorder in Taiwan, 2000-2007

Variable		Adjusted Hazard ratio (95% CI [a])	P value
COPD			
	No	1.00	
	Yes	1.50 (1.43-1.57)	<0.001
Sex			
	Female	1.00	
	Male	0.62 (0.59-0.65)	<0.001
Age (10 years)		1.08 (1.07-1.09)	<0.001
Residence			
	Rural	1.00	
	Urban	0.94 (0.90-0.99)	0.013
Insurance premium			
	Fixed premium and dependent	1.00	
	Less than NTD [b] 20,000	1.04 (0.98-1.10)	0.170
	NTD 20,000 or more	1.05 (1.00-1.11)	0.055
Prednisone, DDD [c]			
	0	1.00	
	1-29	0.69 (0.65-0.73)	<0.001
	30 +	0.51 (0.45-0.58)	<0.001
Depression disorder [d]		2.63 (2.38-2.91)	<0.001
Charlson comorbidity index		0.95 (0.80-1.11)	0.324
Hospital admission days (100 days)		0.92 (0.77-1.08)	0.411
Outpatient (10 visits)		1.18 (1.17-1.19)	<0.001

[a]CI: Confidence interval.

[b] 1USD = 32.1 NTD in 2008

[c] DDD: Define daily dose

[d]ICD-9: 296.20~296.36, 296.82, 300.4, 311

Figure 1 Cumulative incidence of anxiety disorder by study groups (COPD VS Non-COPD). Modified log-rank test p value<0.001.